Remarks

The Office Action of June 10, 2002 has been carefully considered and reconsideration of the application as amended is respectfully requested.

Claims 1-7 are pending in the application. Claims 1-7 were rejected. Claim 1 was objected to. Claim 1 has been amended to correct a typographical error.

The amendments to the claims are not narrowing and are made to expedite the prosecution by eliminating prolonged arguments over matters that are not of concern to our client regarding the patent application and are not directed to the patentability of the claims. They should therefore have no effect on the application of the doctrine of equivalents to the newly amended claims.

Information Disclosure Statement

An Information Disclosure Statement will be filed at a later date.

Drawings

Formal drawings will be filed at a later date.

Claim Objection

Claim 1 was objected to because PD is not the correct symbol for palladium. PD was changed to Pd in claim 1.

Claim Rejection 35 U.S.C. 103(a)

Claims 1-7 were rejected under 35 U.S.C. 103(a) as being unpatentable over Devgan & Bokadia (Aust. J. Chem., 1968, 21, 3001-3003) in view of March (Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, third edition, 1985, pp. 691-700 and 1093-1096).

The Examiner alleges that one having ordinary skill in the art at the time the invention was made would have found it obvious to utilize a conventional hydrogenation process, as taught by March to obtain the di-hydro derivative of β-asarone. Applicants respectfully disagree.

The Examiner also alleges that the skilled artisan would have been further motivated to utilize the conventional process of March to obtain the di-hydro derivative of β-asarone, since the conventional process has already been demonstrated to be effective of a geometric isomer of β-asarone, i.e.γ-asarone, as taught by Devgan et al.. Applicants respectfully disagree.

Asarones exist in nature in three isomeric forms, α-, β- and γ- asarone (trans-2,4,5-trimethoxy-1-propenylbenzene, cis-2,4,5-trimethoxy-1-propenylbenzene and 1-allyl-2,4,5-trimethoxybenzene, respectively). Among these three isomeric forms, α- and γ-asarone are biologically active constituents of various essential oil bearing plants while β-asarone is a recognized toxic compound.

In addition to toxicity, β-asarone has also been proved to be a carcinogenic and has also shown chromosome damaging effect on human lymphocytes *in vitro* after

metabolic activation.

Recent photochemical investigations show that more than 113 compounds are present in *Acorus calamus* which are responsible for the quality and utility of calamus oil. As a result, the diploid and triploid varieties found in North America and Eastern Europe are extensively used for obtaining 1-propyl-2,4,5-trimethoxybenzene. However, the high amounts of toxic and carcinogenic β-asarone in the calamus oil obtained from the tetraploid and hexaploid Asia varieties of *Acorus calamus*, have resulted in these in varieties being internationally prohibited in the flavor, perfumery and human food industries.

A purpose of this invention is to convert the carcinogenic β-asarone to 1-propyl-2,4,5-trimethoxybenzene as described in the present application where the 1-propyl-2,4,5-trimethoxybenzene can be used in the flavor, perfume and human food industries.

The present invention relates to a process for hydrogenating crude calamus oil or β-asarone to obtain asarone free calamus oil which is rich in dihydroasarone (1-propyl-2,4,5-trimethoxybenzene) or pure 1-propyl-2,4,5-trimethoxybenzene. The process of the present invention comprises the steps of (a) providing crude calamus oil or β-asarone in a solvent selected from the group consisting of ethanol, methanol, THF, DCM, toluene and chloroform; (b) hydrogenating the solution obtained in step (a) in the presence of a catalyst selected from the group consisting of Pd/C, Pt, $Pd(OH)_2$, Raney nickel and ammonium formate; at a pressure in the range of 10-40 psi hydrogen gas and at a temperature in the range of 15-40°C; (c) filtering the catalyst and removing the solvent

under reduced pressure in the range of 10-100 mm Hg; and (d) subjecting the reduced calamus oil to column of silica gel chromatography using an eluent to obtain the desired product in liquid form with 85-97% purity.

Devgan et al. does not teach or suggest β-asarone or the toxicity problem associated with β-asarone.

The Devgan & Bokadia article (hereinafter Devgan, et al.) discloses a process for obtaining dihydro γ-asarone from *Acorus calamus* using alcohol and a palladium-charcoal catalyst, removing the alcohol and catalyst, and subjecting the residue to chromatography over neutral alumina and eluting with petroleum, see page 3003 of the Devgan et al. reference.

The Examiner admits that the Devgan et al. reference does not teach or suggest the temperature range and the pressure range for the process defined in the present application. The Examiner relies on the conventional hydrogenation process as described in the March reference to describe the temperature and pressure ranges used in the process defined in the present application.

The March reference teaches hydrogenation of linear alkenes and alkynes.

The temperature and pressure ranges defined in the claims of the present application are specific so as to achieve hydrogenation of the double bond located on the substituent of the benzene ring. The hydrogenation process as defined in the present

application does not affect the double bonds located within the benzene ring.

The March reference does not describe a pressure range of 10-40 psi as defined in the process of the present invention. The March reference states that hydrogenation is carried out at just above atmospheric pressure but that some double bonds are more resistant and require higher pressure, see the first paragraph on page 693 of the March reference. The March reference does not describe the pressure ranges to be used and does not specify which double bonds are more resistant and require higher pressure.

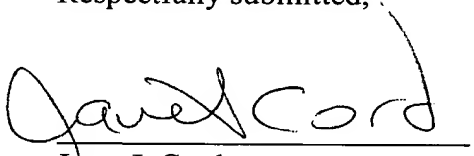
The temperature range described in the March et al. reference is 0 to 275°C. The temperature range defined in the March reference is too broad of a range to determine a temperature range useful for hydrogenation of alkenes attached as substituents on an aromatic ring.

The March reference states that "it is usually possible to find conditions under which double bonds can be reduced selectively", see page 692 of the March reference. However, the March references does not further specify a temperature range which would selectively reduce an alkene attached as a substituent on an aromatic ring.

Therefore, to one having ordinary skill in the art the claimed process for preparing 1-propyl- 2,4,5- trimethoxybenzene would not be obvious in view of a combination of references that do not disclose or suggest hydrogenation of β-asarone and disclose only hydrogenation of linear alkenes and alkynes.

In light of the above, Applicants submit that all rejections and objections of record have been overcome. Applicants accordingly submit that the application is now in condition for allowance and respectfully request action in accordance therewith.

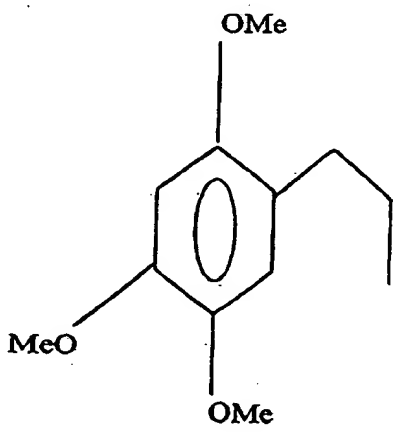
Respectfully submitted,



Janet I. Cord
LADAS & PARRY
26 West 61st Street
New York, NY 10023
Reg. No. 33,778 (212) 708-1935

MARKED-UP COPY

1. (Twice amended) A process for the preparation of 1-Propyl-2,4,5-trimethoxybenzene of the formula I [useful as an aroma molecule and as a starting material and intermediate for preparation of various drugs,] :



the process comprising the steps of:

(a) providing crude calamus oil or β-asarone in a solvent selected from the group consisting of ethanol, methanol, THF, DCM, toluene and chloroform;

(b) hydrogenating the solution obtained in step (a) in the presence of a catalyst selected from the group consisting of [PD/C] Pd/C, Pt, $Pd(OH)_2$, Raney nickel and ammonium formate; at a pressure in the range of 10-40 psi hydrogen gas and at a temperature in the range of 15-40°C;

(c) filtering the catalyst and removing the solvent under reduced pressure in the range of 10-100 mmHg; and

(d) subjecting the reduced calamus oil to column of silica gel chromatography using an eluent to obtain the desired product in liquid form with 85-97% purity.